

# Exhibit 112

Review

## Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-analysis

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### Abstract

**Introduction:** The asbestos and ovarian cancer relationship is not well understood because of small numbers of women exposed to asbestos, small numbers of cases, and misclassification of peritoneal mesothelioma as ovarian cancer on death certificates. The aim of this study was to conduct a meta-analysis to quantify the evidence that exposure to asbestos causes ovarian cancer.

**Methods:** Fourteen cohort and two case-control studies were identified in Medline searches from 1950 to 2008.

**Results:** Statistically significant excess mortality was reported in four of the cohort studies, all of which determined their outcomes from the death certificate. Peritoneal mesotheliomas were reported in these studies, two of which reexamined pathology specimens and reported disease misclassification. Exposure-response relationships were inconsistent. When all studies were included in a meta-analysis, the effect size was 1.75 (95% CI, 1.45–2.10) attenuating to 1.29 (95% CI, 0.97–1.73) in studies with confirmed ovarian cancers.

**Conclusion:** Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. This result may have occurred because of disease misclassification. *Cancer Epidemiol Biomarkers Prev*; 20(7); 1287–95. ©2011 AACR.

### Introduction

In May 2009, a summary of the latest assessment of the carcinogenicity of metals, arsenic, dusts, and fibers, including asbestos, by the International Agency for Research on Cancer (IARC) Monograph Working Group was published in the *Lancet Oncology* (1). For the first time, the evidence was declared sufficient in humans to show that exposure to asbestos causes cancer of the ovary (2). It has long been established that exposure to asbestos causes malignant mesothelioma, lung cancer, and asbestosis, as well as "benign" pleural diseases. Excess mortality and incidence of these diseases have been shown repeatedly in cohorts of occupationally exposed workers and exposure-response relationships have shown a clear causal relationship between asbestos exposure and mesothelioma, lung cancer, and asbestosis (3–6). However, the IARC Monograph that will

provide the evidence supporting the sufficient ruling has not yet been published.

The relationship between asbestos exposure and ovarian cancer is not as well understood as that of asbestos-related diseases. Studies that have examined this issue have been limited for 2 major reasons:

1. Small numbers of cases: Much fewer women than men have been exposed to asbestos, particularly in more heavily exposed occupational settings where relative risks are higher. Although many women in epidemiologic studies have had domestic or general environmental exposure, levels have generally been relatively low so that risks and hence numbers of cases have also been few.
2. Difficulties with diagnosis: Many of the studies that have reported excess ovarian cancer following asbestos exposure have examined mortality from ovarian cancer and used the cause of death as listed on the death certificate to identify the cause of death. The accuracy of death certificates has been questioned repeatedly (7, 8), particularly in relation to asbestos-related diseases (9). Pleural mesothelioma has a long history of being misreported on death certificates most often being labeled as lung or pleural cancer (3, 9, 10). It has been particularly difficult to distinguish between peritoneal mesothelioma and ovarian serous carcinoma. Immunohistochemical tests to aid in the identification of mesothelioma cells became available in 1996–1997 with

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the introduction of calretinin. Since then, many new markers have become available, although none of these are useful in distinguishing between ovarian cancer and peritoneal mesothelioma. A recent review of the value of immunohistochemistry to distinguish between peritoneal mesothelioma and serous carcinoma of the ovary and peritoneum concluded that "positive serous carcinoma markers, by and large, have a higher degree of sensitivity and specificity in assisting in discriminating between these malignancies than the positive mesothelioma markers. From a practical point of view, a combination of MOC-31 (or BER-EP4), estrogen receptors, and calretinin immunostaining should allow a clear distinction to be made between epithelioid peritoneal mesotheliomas and serous carcinomas in most cases (11)."

Accordingly, peritoneal mesothelioma has often been listed on the death certificate as stomach, colon, or ovarian cancer or carcinomatosis (9, 12–14).

However, there are biologically plausible reasons as to why exposure to asbestos may cause ovarian cancer. Asbestos fibers have been found in the ovaries of women who were exposed to asbestos in the Norwegian pulp and paper industry and also among women whose household contacts worked with asbestos (15, 16), although possible sample contamination cannot be ruled out. The mode of distribution of the fibers through the body following inhalation is not well understood. The fibers may migrate across the diaphragm through the peritoneal cavity and penetrate the ovaries. Animal studies have observed asbestos fibers within the cytoplasm of epithelial and interstitial cells within 24 hours after brief inhalation (17). Once fibers have entered the interstitium, they then have access to the vascular and lymphatic systems. Fibers in the lymphatic system can be channeled to the visceral pleura and subsequently to the pleural cavity. Mechanical irritation leading to fibrosis or to cancer, or "frustrated phagocytosis" (where the macrophage is damaged because it is unable to digest the whole asbestos fiber because of its length), thus leading to the production of hydroxyl radicals and reactive oxygen species that induce cell injury (18, 19), are 2 mechanisms by which the fibers may cause cancer once they reach the ovary. Experiments in which 10 g of tremolite mixed with 400 mL of water was injected intraperitoneally into mice, hamsters, guinea pigs, and rabbits showed that in 2 of 10 rabbits and 2 of 16 guinea pigs, the abnormality that developed in the epithelium of the ovary resembled lesions observed in early human ovarian cancers (20). "Overall, the available evidence in favor or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (21).

The aims of this study were (1) to review the epidemiologic studies that have reported effect estimates for ovarian cancer incidence or mortality in women following exposure to asbestos and (2) to conduct a meta-

analysis of those studies to quantify whether that exposure to asbestos causes ovarian cancer.

## Methods

Studies were identified through a systematic review of the literature available on MEDLINE from 1950 to December 2008. The database was searched using combinations of the search terms "women" or "females" or "girls" and "asbestos" or "fibres" or "dust" or "crocidolite" or "chrysotile" or "amosite" or "occupational exposure" or "environmental exposure" or "household exposure" or "neighbourhood exposure" or "residential exposure" or "locational exposure" or "domestic exposure" or "familial exposure" or "exposure" with one of the following outcomes "cancer" or "mortality" or "death" or "neoplasms" or "ovarian cancer." Any cohort or case-control study that examined women and asbestos exposure and was published in English was included. Studies were also identified from references listed in published articles. Case reports were not included.

Summary effect estimates were examined using the *metan* suite of commands in Stata 10.1 (22, 23). Models that assumed that the study populations were all relatively homogenous (fixed effects) and models that assumed that the true exposure-related risks in each study vary randomly (random effects) were examined and both are reported. All studies described in Table 1 were included in the meta-analysis. Expected deaths [based on the number of observed deaths and the standardized mortality ratios (SMR)] and 95% Confidence Intervals (95% CI) were calculated for the study of Polish women diagnosed with asbestosis, which did not include them in their published article (24). Forest plots were produced automatically as part of the *metan* suite of commands in Stata 10.1.

## Results

Fourteen cohort (3, 12, 24–34) and 2 case-control (35, 36) studies of women exposed to asbestos in their jobs or from their general environment and that examined ovarian cancer incidence or mortality as an outcome were identified from the literature (Table 1). Four of the cohort studies had been reported on several times over their years of follow-up: In each case, only the latest report is shown in the table and included in the meta-analysis (3, 12, 26, 28).

Generally, the number of cases of ovarian cancer reported in the cohort studies was small, ranging from 1 case [among Polish women diagnosed with asbestosis (24) and Turin textile workers (29)] to 12 cases reported among Leyland crocidolite gas mask workers (25). However, 5,072 cancer cases were reported among the whole Finnish female working population born between 1906 and 1945 in which exposure to asbestos was determined from a job exposure matrix (33). The case-control studies had more cases than the cohort studies: 69 cases reported

**Table 1.** Cohort and case-control studies of women exposed occupationally or environmentally to asbestos that examine ovarian cancer mortality or incidence as an outcome

Study	Author (ref)	Publication year	Number of women exposed	Type of asbestos exposure	Period of follow-up	Peritoneal mesothelioma cases (n)	Pleural mesothelioma cases (n)	Ovarian cancer cases (n)	SMR (95% CI)	Ovarian cancers confirmed
<b>Cohort studies</b>										
Leyland gas mask workers	Acheson et al. (25)	1982	757	Crocidolite	1951–1980	2	15 <sup>a</sup> (5)	12	2.75 (1.42–4.81)	No
Blackburn gas mask workers	Acheson et al. (25)	1982	570	Chrysotile	1951–1980	0	7 <sup>a</sup> (1)	5	1.48 (0.48–3.44)	No
Employees on central register, Germany	Rosler et al. (32)	1994	616	Chrysotile and crocidolite	1977–1988	4	9	2	1.09 <sup>b</sup> (0.13–3.95)	No
Italian women compensated for asbestosis	Germani et al. (27)	1999	631	Chrysotile and crocidolite	1980–1997	12	14	9	4.77 (2.18–9.06)	No
Population of Finnish female workers	Vasama-Neuvonen et al. (33)	1999	892,591 (born between 1906 and 1945)	Not stated	1971–1995	N/A	N/A	5,072	SIR = 1.3 (0.9–1.8) <sup>e</sup>	Yes
East London asbestos factory workers	Berry et al. (3)	2000	700	Crocidolite and chrysotile	1951–1980	11	14	9	2.53 (1.16–4.80)	Yes—earlier report (13)
Polish women diagnosed with asbestosis	Szeszenia-Dabrowska et al. (24)	2002	490	Not stated	1970–1999	0	3 <sup>d</sup>	1	0.79	No
Turin asbestos textile factory workers	Mamo et al. (29)	2004	645	Chrysotile	1981–1995	0	10	1	1.28 (0.02–7.12)	No
Polish asbestos cement products factory workers	Wilczynska et al. (34)	2005	1,470	Not stated	1945–1999	0	3	8	1.76 (0.76–3.47)	No
<b>Case-control studies</b>										
Italian asbestos textile workers	Pira et al. (30)	2005	3,76 <sup>f</sup> (1,38–8,18) 1,077	Mixed with crocidolite	1946–1996	9 <sup>c</sup>	11 <sup>d</sup>	5	2.61 (0.85–6.09)	No

(Continued on the following page)

**Table 1.** Cohort and case-control studies of women exposed occupationally or environmentally to asbestos that examine ovarian cancer mortality or incidence as an outcome (Cont'd)

Study	Author (ref)	Publication year	Number of women exposed	Type of asbestos exposure	Period of follow-up	Peritoneal mesothelioma cases (n)	Pleural mesothelioma cases (n)	Ovarian cancer cases (n)	SMR (95% CI)	Ovarian cancers confirmed
Nottingham gas mask workers	McDonald et al. (12)	2006	1,154	Crocidolite	1940–2002	18	47	10	1.8 (0.9–3.3)	Yes—earlier report (14)
Italian asbestos cement factory workers	Magnani et al. (28)	2007	777	Chrysotile and crocidolite	1965–2003	16 <sup>c</sup>	39 <sup>d</sup>	9	2.27 (1.04–4.32)	Yes
Italian wives of asbestos factory workers	Ferrante et al. (26)	2007	1,780	Chrysotile and crocidolite	1965–2003	3 <sup>c</sup>	21 <sup>d</sup>	11	1.42 (0.71–2.54)	No
Wittenoom women	Reid et al. (31)	2009	2,968	Crocidolite	1982–2006	1	46	11	SIR = 1.27 (0.52–2.02)	Yes
Case-control studies										
Johns Hopkins Hospital patients <sup>g</sup>	Rosenblatt et al. (36)	1992	77 cases 46 controls	Not stated	1981–1985	N/A	N/A	69	1.3 (0.3–3.6) respiratory exposure 2.8 (0.9–8.8) relatives exposed to fibers	Yes
Norwegian pulp and paper workers (nested case-control study)	Langseth et al. (35)	2004	46 cases 184 controls	Not stated	1953–1999	N/A	N/A	6	2.02 (0.72–5.66)	Yes

<sup>a</sup>Lung and pleural cancers combined (number of mesotheliomas listed on death certificates in this cohort).

<sup>b</sup>Standardized proportionate mortality ratio.

<sup>c</sup>Peritoneal cancers.

<sup>d</sup>Pleural cancers.

<sup>e</sup>Medium/high exposure.

<sup>f</sup>Among women who worked in asbestos yarn and cloth production areas (high exposure).

<sup>g</sup>Fibers include asbestos, talc, and fiberglass.



some respiratory exposure to asbestos and 18 cases reported relatives with occupational asbestos exposure among participants of the Johns Hopkins study. Among Norwegian pulp and paper mill workers, there were 6 cases who had worked in areas where they were likely to have been exposed to asbestos.

Statistically significant excess mortality or incidence of cancer of the ovary was reported in 4 of the 14 cohort studies. SMRs and their 95% CIs in these 4 studies ranged from 4.77 (95% CI, 2.18–9.06) to 2.27 (95% CI, 1.04–4.32; refs. 3, 25, 27, 28). Of the remaining 10 cohort studies, 5 reported a tendency to excess mortality, although SMR estimates were unstable, ranging from 2.61 (95% CI, 0.85–6.09) to 1.42 (95% CI, 0.71–2.54). Women who worked in asbestos yarn and cloth production in a Polish asbestos cement products factory had a statistically significant excess mortality from ovarian cancer [SMR = 3.76 (95% CI, 1.38–8.18)], although the association was not significant over all the female factory workers (12, 25, 26, 30, 34). Five studies reported ovarian cancer incidence or mortality around the same population as their reference populations (24, 29, 31–33). Both case-control studies reported a nonsignificant excess incidence with asbestos exposure. Women with relatives with occupational asbestos exposure reported a nonsignificant but 3-fold risk of ovarian cancer, although the overall risk for all women in that study was close to unity (35, 36).

The type of asbestos to which the women were exposed was crocidolite (blue asbestos—the most mesotheliogenic of the asbestos fibers; ref.37) only in 3 cohorts (12, 25, 31), chrysotile (white asbestos) only in 2 (25, 29), chrysotile and crocidolite in 5 cohorts (3, 26–28, 32), mixed fibers including crocidolite in 1 cohort (30), and 4 studies (including the 2 case-control studies) did not report the fiber type (24, 34–36). The remaining study of economically active Finnish women born between 1906 and 1945 had their probability of asbestos exposure determined on the basis of their job titles, as reported in the 1970 census and a job exposure matrix (the FINJEM; ref. 38): the types of asbestos were not distinguished, although anthophyllite was mined and widely used throughout Finland (39). Four of the studies that reported a significant excess risk of ovarian cancer reported exposure to crocidolite or chrysotile and crocidolite.

Small numbers of cases or lack of exposure information inhibited the examination of exposure-response relationships and mortality or incidence of ovarian cancer. Nevertheless, 3 studies (3, 14, 28) examined SMRs by category of exposure (low/medium/high), duration of employment (years), or latency (time between first exposure to asbestos and onset of disease), and 1 examined ovarian cancer incidence and quantitative asbestos exposure characteristics by using a nested case-control design and conditional logistic regression (31). Among East London factory workers, there was a significant overall excess of ovarian cancers, but when examined by category and duration of exposure, the trend was not significant ( $P = 0.18$ ). However, the excess was significant

among women who had "severe" exposure for more than 2 years (3). A nonstatistically significant exposure trend with duration of exposure was observed among Italian factory workers; 0 cases: <1 year, SMR = 2.4, 1–4 years; 0 cases: 5–9 years, SMR = 2.7, 10–19 years; SMR = 2.8, 20–29 years; and SMR = 2.9,  $\geq 30$  years (28). Exposure-response relationships were examined in an earlier report of the Nottingham gas mask workers. Mortality from ovarian cancer was higher among women exposed for more than 1 year [observed/expected (O/E) 3/0.95] than among those exposed for less than 1 year (O/E 2/1.13; ref. 14). Several quantitative measures of asbestos exposure, including intensity (f/mL), duration of employment or residence, and time since first exposure, were not associated with the incidence of ovarian cancer among the Wittenoom women (31).

Twelve of the cohort studies listed in Table 1 examined mortality from ovarian cancer and relied on the cause of death as listed on the death certificate. In addition, cases of peritoneal mesothelioma were observed in 8 of these studies, suggesting that misclassification of peritoneal mesothelioma as ovarian cancer may have occurred.

Cases of peritoneal mesothelioma were reported in 4 of the studies that reported a statistically significant excess mortality from ovarian cancer (3, 25, 27, 28). Two of these studies attempted to confirm the diagnosis of ovarian cancer pathologically. Among East London factory workers, ovarian cancer was confirmed in 2 cases with material available (from a total of 4 ovarian cancers up to 1968; ref.13). Two cases listed as carcinomatosis were confirmed as ovarian cancers, and 1 case listed as ovarian cancer was determined to be a peritoneal mesothelioma (13). The latest follow-up to 1980 reported 9 cases of ovarian cancer, but it is not clear how many of these were confirmed histologically (3). Among Italian asbestos cement workers, 7 of 9 cases were confirmed as ovarian cancers (28). Three cohort studies reported a statistically significant excess rate of ovarian cancer but did not reexamine ovarian cancer pathology specimens. One of these (Italian women compensated for asbestosis; ref. 27) had more cases of peritoneal mesothelioma than ovarian cancer, suggesting that misclassification may have occurred. Among Leyland gas mask workers exposed to crocidolite, there were 2 cases of peritoneal mesothelioma and 12 cases of ovarian cancer. The authors suggested that ovarian cancers might have been peritoneal mesotheliomas misclassified (25). There were no reported cases of peritoneal mesothelioma among Polish asbestos cement products factory workers compared with 8 cases of ovarian cancer (34). Misclassification of disease is important to the internal validity of these studies, as with small numbers of cases of ovarian cancer, any misclassification could overestimate (or underestimate) the reported association with asbestos exposure.

Five studies that did not find a statistically significant excess rate of ovarian cancer reexamined ovarian cancer pathology where available. In an earlier report on the Nottingham crocidolite gas mask workers, of 6 ovarian cancer deaths, 2 were confirmed as ovarian cancers and 1

was determined to be a peritoneal mesothelioma. Material was not available on the other 3 cases (14). The latest report of this cohort by McDonald and colleagues could not further review ovarian cancer pathology as only cause of death codes were available (12). Among the Wittenoom women, specimens from 9 cases of ovarian cancer were available for reexamination from a total of 16 cases. All 9 cases were confirmed as ovarian cancers (31). Similarly, all cases of ovarian cancer were confirmed among Finnish women defined as exposed to asbestos from a job exposure matrix as well as the 2 case-control studies (33, 35, 36).

Confounding and independent risk factors for ovarian cancer have not been addressed well in most studies, predominantly because they have been retrospective studies of occupational cohorts and limited data on potential confounders were available. Only 3 of the studies (the 2 case-control studies and the cohort of economically active Finnish women) assessed any of the following variables: age at menarche or menopause, late first pregnancy and age at first delivery, use of oral contraceptives, or tubal ligation, all known to be independent risk factors for ovarian cancer. Although few studies have collected data on these other risk factors, this may not have influenced the findings significantly, as they are unlikely to be associated with asbestos exposure and therefore are not likely to confound any association.

Loss to follow-up was a significant problem for 3 studies; all reporting more than 20% loss to follow-up (3, 31), with the highest reporting 33% (12). In an attempt to overcome this loss, one of the studies stopped accruing person-years at risk for those lost to follow-up from the date they were last known to be alive, thus underestimating person-years at risk and overestimating the SMR (31). Berry and colleagues did not state how they censored those

lost to follow-up (3), but in an earlier report, Newhouse and colleagues censored those lost to follow-up on their last date of employment, so underestimating person years at risk and thus overestimating the SMR (13). McDonald and colleagues presented 2 sets of results, 1 for the complete cohort and 1 for a subset with more complete follow-up. SMRs were slightly larger among the more complete subset than those for the whole cohort (12). High loss to follow-up may over- or underestimate the risk of disease following exposure to asbestos, depending on the type of censoring method used to account for the loss to follow-up.

The meta-analysis that examined all studies showed a 75% excess risk of ovarian cancer in women who had been exposed to asbestos (Table 2). The effect size was similar between the models that assumed no heterogeneity between the studies (fixed effects) and those that assumed the exposure-related risks differed randomly between the studies (random effects). Figure 1 shows the corresponding forest plot for both the fixed- and random-effects models for all studies combined. The analyses were repeated for all cohort studies only and case-control studies only and similar effects were observed, although the effect was not statistically significant in the case-control studies (Table 2). When only those studies that confirmed their ovarian cancer pathology were included in a meta-analysis, the effect estimate declined, although remained statistically significant. The effect declined again and was not statistically significant when those studies that examined cancer incidence were included in a meta-analysis. These 4 studies did not rely on cause of death information from the death certificates to classify their cases.

A meta-analysis conducted on 9 of the cohort studies (12, 24, 26–31, 34) that also reported SMRs and 95% CIs (or provided enough information so that they could be calculated) for mesothelioma gave a fixed-effects size of 70.9

**Table 2.** Summary statistics for asbestos exposure and incidence or mortality from ovarian cancer

	Number of studies	Number of cases	Fixed-effects size (95% CI)	Random-effects size (95% CI)	Heterogeneity, $\chi^2$	Heterogeneity, degrees of freedom	Heterogeneity, P
All studies combined	16	5,240	1.75 (1.45–2.10)	1.80 (1.45–2.24)	17.91	15	0.268
Cohort studies only	14	5,165	1.75 (1.45–2.12)	1.83 (1.44–2.33)	17.61	13	0.173
Case-control studies only	2	75	1.69 (0.76–3.73)	1.69 (0.76–3.73)	0.29	1	0.593
All studies that reviewed ovarian pathology	7	5,186	1.54 (1.22–1.95)	1.54 (1.22–1.95)	5.72	6	0.455
Cohort studies that reviewed ovarian pathology	5	5,102	1.53 (1.20–1.95)	1.59 (1.17–2.15)	5.38	4	0.251
Studies that examined cancer incidence	4	5,158	1.29 (0.97–1.73)	1.29 (0.97–1.73)	1.08	3	0.781

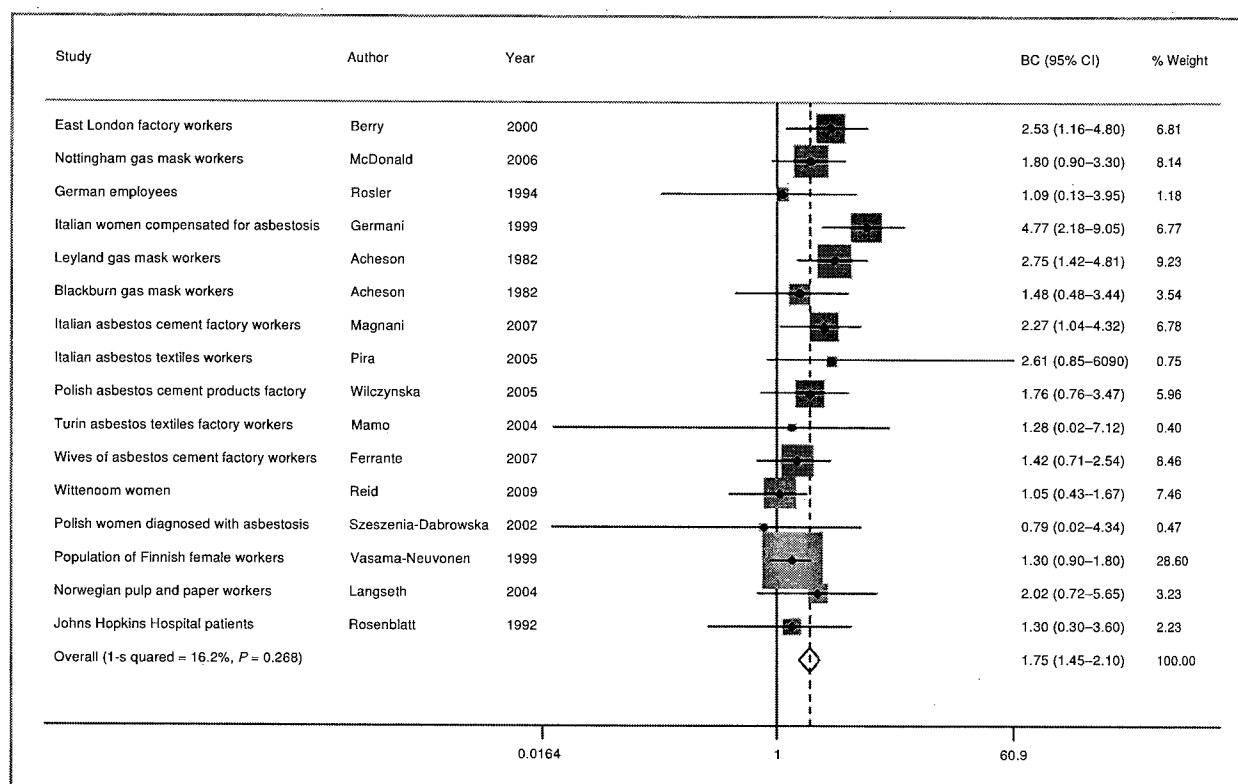


Figure 1. Forest plot of fixed summary effect for ovarian cancer and asbestos exposure.

(95% CI, 61.4-82.0) and random-effects size of 63.2 (95% CI, 41.9-95.3; data not shown). Figure 2 shows the relationship between standardized mortality or incidence ratios for mesothelioma and ovarian cancer for the 9 cohort studies that examined both mesothelioma and ovarian cancer included in the mesothelioma meta-analysis. There is clearly no relationship between the two. When the exposure is sufficient to have caused mesothelioma, there is no corresponding increased risk in ovarian cancer.

## Discussion

Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. This result was obtained when all studies were included in the meta-analysis and again when only those studies that had reexamined ovarian cancer pathology were included. Only the meta-analysis of those studies that reported ovarian cancer incidence (i.e., those studies that did not rely on cause of death certification to classify their cases of ovarian cancer) did not observe a significant excess risk.

In the studies that did not examine ovarian cancer pathology, or confirmed cases of mesothelioma from a cancer or mesothelioma registry, misclassification of the cause of death in some cases is likely to have occurred,

given that misclassification was reported in those studies that did reexamine cancer pathology specimens. Misclassification may result in an underestimate of peritoneal mesothelioma and an overestimate of ovarian cancer or the converse. Among women, peritoneal mesothelioma may be more likely to be classified as ovarian, colon, or stomach cancer, rather than a rare occupational cancer. The cohort study referred to in the *Lancet* summarizing the IARC reclassification (women gas mask workers) did not reexamine pathology (25). An examination of cancer

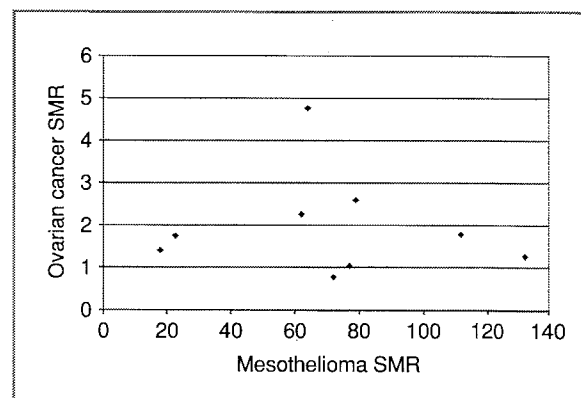


Figure 2. Relationship between mesothelioma and ovarian cancer-standardized mortality ratios for 9 cohort studies presented in Table 1 (3-6, 9, 27, 28, 31, 36)



incidence (and its use of cancer registration rather than death certification for disease outcome data) may have produced different results. Notably, the meta-analysis on the 2 case-control and 2 cohort studies that examined ovarian cancer incidence did not report a statistically significant excess risk of ovarian cancer.

The IARC makes its determinations of cancer causality (if an observed association between an exposure and a disease is causal) by using Bradford Hill's suggested hierarchy of criteria (40, 41). The first of these was the strength of the association. In this review, the greatest risk of ovarian cancer was observed among Italian women compensated for asbestosis. Their risk was almost 5-fold compared with their reference population (SMR = 4.77). However, their SMR for peritoneal mesothelioma was 40.9 and for pleural mesothelioma was 64.0, between 8 and 13 times larger than that observed for ovarian cancer (27). The effect size from the meta-analysis for ovarian cancer ranged from 1.29 among those studies that examined cancer incidence to 1.85 for all cohort studies. The effect size for mesothelioma was 70.9 (95% CI, 61.4–82.0). Clearly, the effect size for mesothelioma, a disease known to be caused by exposure to asbestos, is much larger than that for ovarian cancer. Also, if there was misclassification of mesothelioma and ovarian cancer, then some relationship between the 2 SMRs shown in Figure 2 is likely to have been observed. Similarly, if there was an exposure-response relationship, then some relationship between the SMRs should have been observed. Another explanation for the lack of correlation between mesothelioma and ovarian cancer SMRs is that asbestos exposure does not cause ovarian cancer.

Hill's second criterion for causality was consistency—that the observed association been repeated in different people, places, and times (40). The present study has shown that 4 of 14 cohort studies reported a statistically significant excess rate for ovarian cancer among women exposed to asbestos. Of the remaining 10 studies, 5 reported a tendency to excess but failed to reach statistical significance and 5 reported rates that were similar to those of their reference populations. Strong evidence of consistency was not observed among these studies, although no study reported any protective effect.

Also included in Hill's criteria for causation was biological gradient or demonstration of an exposure-response relationship (40). In the studies presented in this article, examination of exposure-response relationships was limited because of the small numbers of cases of ovarian cancer. Most of the studies were limited by small numbers of women both in terms of the number of women exposed to asbestos and the subsequent small

numbers of ovarian cancers. However, where exposure-response relationships were examined, they were inconsistent. No study showed a statistically significant trend of ovarian cancer with degree of asbestos exposure. In addition, there was no evidence of a significant trend across studies as grouped exposure increased (see Fig. 2).

Other Hill's criteria are temporality (which is met because disease follows exposure) and specificity (which Hill largely discounts: It is known that asbestos causes more than one disease). Plausibility, coherence, and analogy are all satisfied, and experiment is not really applicable.

## Conclusion

Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. However, this finding may result from the methods used to identify the ovarian cancer cases. Where disease outcome was identified from the cause of death as listed on the death certificate, given the small numbers of ovarian cancer cases in each study, even misclassification of 1 cancer may exert a large impact on the exposure effect. The meta-analysis of those studies that examined ovarian cancer as determined on the death certificate reported an excess risk. In contrast, no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases were ascertained from a cancer registry. The IARC Monograph that contains the evidence supporting its sufficient ruling that asbestos exposure causes ovarian cancer is not yet in the public domain. However, the authors of this article suggest that the IARC decision to determine asbestos exposure as a cause of ovarian cancer was premature and not wholly supported by the evidence. Meta-analysis techniques cannot account or adjust for the quality of the data contained in the original studies that are used in the meta-analysis. If the original data contain errors of classification, then errors are built into the meta-analysis.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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